D860057/S011

Summary of Safety and Effectiveness Data
Carpentier-Edwards PERIMOUNT Pericardial Bioprosthesis Model 6900 Mitral
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1. GENERAL INFORMATION

Device Generic Name:	Replacement Heart Valve
Device Trade Name:	Carpentier-Edwards PERIMOUNT Pericardial Bioprosthesis Model 6900 Mitral
Applicant's Name and Address:	Edwards Lifesciences LLC One Edwards Way Irvine, CA 92614
PMA Application Number:	P860057/S11

Date of Notice of Approval to the Applicant:

2. INDICATIONS FOR USE

The Carpentier-Edwards PERIMOUNT Pericardial Bioprosthesis Model 6900 Mitral is indicated for patients who require replacement of their native or prosthetic mitral valve.

3. DEVICE DESCRIPTION

The Carpentier-Edwards PERIMOUNT Pericardial Bioprosthesis Model 6900 Mitral is a trileaflet stent-supported bioprosthetic valve comprised of bovine pericardium mounted on a flexible frame. The bioprosthesis is treated according to the Edwards XenoLogiX process, which uses ethanol and polysorbate-80 (a surfactant), and is packaged and terminally sterilized in glutaraldehyde. Glutaraldehyde is shown to both reduce the antigenicity of tissue xenograft valves and increase tissue stability; however, glutaraldehyde has not been shown to affect or reduce the calcification rate of the valve.

The Carpentier-Edwards PERIMOUNT Pericardial Bioprosthesis Model 6900 Mitral is designed for the mitral position and is available in the following external sewing ring diameters: 25 mm, 27 mm, 29 mm, 31 mm, and 33 mm.

The flexible frame or wireform of the valve is composed of Elgiloy and is covered with a woven polyester cloth. It is designed to be compliant at the orifice and commissures to reduce the closing loading shocks at the commissure tips and free margin of the leaflets.

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An Elgiloy band attached to a polyester film band surrounds the base of the wireform frame, providing structural support for the orifice and identification radiologically. A suture ring covered with polytetrafluoroethylene (PTFE) cloth is attached to the wireform frame. The suture ring contains inserts of silicone rubber and non-woven polyester.

4. CONTRAINDICATIONS

None known.

5. WARNINGS AND PRECAUTIONS

5.1. Warnings

FOR SINGLE USE ONLY.

DO NOT RESTERILIZE THE VALVE BY ANY METHOD. Exposure of the bioprosthesis or container to irradiation, steam, ethylene oxide, or other chemical sterilants will render the bioprosthesis unfit for use.

DO NOT FREEZE OR EXPOSE THE VALVE TO EXTREME HEAT. Each bioprosthesis in its jar is shipped in a molded foam enclosure containing two temperature indicators, which are intended for monitoring the temperature to which the device is exposed during transit. If either indicator has been activated, indicating that the valve has been exposed to freezing temperatures or has had prolonged exposure to heat, do not use the valve. Please refer to the **Storage** section for further instructions.

WARNING: Studies have NOT been performed to evaluate the safety or compatibility of this bioprosthesis during magnetic resonance imaging (MRI) scans. As such, the potential hazards of MRI procedures on patients receiving this bioprosthesis are unknown.

WARNING: Accelerated deterioration due to calcific degeneration of the bioprosthesis may occur in:

- children, adolescents, or young adults;
- patients with abnormal calcium metabolism (e.g., chronic renal failure or hyperparathyroidism).

5.2. Precautions

- The outside of the jar is not sterile and must not be placed in the sterile field.
- Do not use the bioprosthesis if the tamper evident seal is broken.
- Do not use the bioprosthesis if the container is leaking, damaged, or the glutaraldehyde solution does not completely cover the bioprosthesis.
- Adequate rinsing with physiological saline must be performed before implantation to reduce the glutaraldehyde concentration.
- Do not expose the valve to any solutions, chemicals, antibiotics, or other drugs, except for the storage solution or sterile physiological saline solution, as irreparable damage to the leaflet tissue may result that is not apparent under visual inspection.

- Do not allow the valve tissue to dry. It must be kept moist at all times. Maintain tissue moisture with sterile physiological saline irrigation on both sides of the leaflet tissue.
- Do not pass catheters, transvenous pacing leads, or any surgical instrument across the valve since they may cause tissue damage.
- Care must be taken when performing open and closed chest cardiac massage in patients with an open strut mitral prosthesis due to the increased risk of ventricular perforation.

CAUTION: Glutaraldehyde may cause irritation of the skin, eyes, nose, and throat. Avoid prolonged or repeated exposure or breathing of the solution. Use only with adequate ventilation. If skin contact occurs, immediately flush the affected area with water. In the event of contact with the eyes, seek immediate medical attention. For more information about glutaraldehyde exposure, please refer to the Material Safety Data Sheet MSDI0424 available from Edwards Lifesciences.

6. ALTERNATIVE PRACTICES AND PROCEDURES

The surgical replacement alternative to the Carpentier-Edwards PERIMOUNT Pericardial Bioprosthesis Model 6900 Mitral is surgical replacement of the malfunctioning mitral valve with an allograft or another prosthetic replacement heart valve for which there is an approved premarket approval application (PMA). When a replacement heart valve is chosen as the appropriate therapy, the option of choosing between a mechanical or biological prosthesis exists. The choice of replacement heart valve depends on an assessment of patient factors which include age, preoperative condition, cardiac anatomy, and the patient's ability to tolerate long-term anticoagulant therapy.

Other forms of treatment may include the use of cardiac drug therapy or other types of surgical treatment, such as native valve reconstruction or modification (e.g., annuloplasty).

7. MARKETING HISTORY

Currently the device is distributed in Algeria, Argentina, Australia, Austria, Bangladesh, Barbados, Belgium, Brunei, Canada, Chile, China, Columbia, Costa Rica, Cyprus, Czech Republic, Denmark, Ecuador, Egypt, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Indonesia, Ireland, Israel, Italy, Japan, Jordan, South Korea, Lebanon, Luxembourg, Malaysia, Malta, Mexico, Morocco, Netherlands, New Zealand, Norway, Pakistan, Philippines, Portugal, Qatar, Slovak Republic, Romania, Russia, Singapore, Slovenia, South Africa, Spain, Sri Lanka, Sweden, Switzerland, Taiwan, Thailand, Tunisia, Turkey, Yugoslavia, and the United Kingdom.

The Carpentier-Edwards PERIMOUNT Pericardial Bioprosthesis Model 6900 Mitral has not been withdrawn from marketing in any country for any reason relating to the safety and/or the effectiveness of the device.

8. ADVERSE EVENTS

Three (3) multi-center, non-randomized, prospective, non-US clinical studies were conducted of patients implanted with the Carpentier-Edwards PERIMOUNT Pericardial Bioprosthesis Model

6900 Mitral. Three hundred-one (301) patients had isolated mitral valve replacement (MVR) and 62 patients had double valve replacement (DVR), where the aortic valve was replaced with a Carpentier-Edwards Pericardial Bioprosthesis aortic model. One study was conducted between 1984 and 1986, the second study was conducted between 1989 and 1994, and the third study was conducted between 1996 and 1997. Patients were evaluated preoperatively, intraoperatively/at discharge, at 1 year, and annually thereafter. Adverse events were captured throughout the postoperative period.

Table 1 presents the observed rates for early events (≤ 30 days), the linearized rates for late events (> 30 days postoperatively), and the actuarial adverse event rates at 1, 5, and 8 years postoperatively.

The adverse event rates were based on 363 patients at 9 centers. The cumulative follow-up was 1100 patient-years with a mean follow-up of 3.0 years (SD = 2.4 years, range = 0 to 8.2 years).

Table 1: Observed Adverse Event Rates for MVR and DVR
All patients analyzed: N= 363 Cumulative follow-up: 1100 patient-years

	Early Events		Late Events[1]		Freedom from Event (%) [95% CI][2]		
Complication	n[3]	%	n	%/pt-yr	1 year (n = 363)	5 years (n = 141)	8 years (n = 18)
Mortality (all)	34	9.4	50	4.7	85.5 [81.8, 89.2]	75.4 [70.3, 80.6]	65.4 [57.6, 73.2]
Major adverse events							
Mortality (valve-related)	0	0	16	1.5	97.7 [96.0, 99.4]	95.3 [92.8, 97.8]	91.9 [87.5, 96.4]
Explants	0	0	8	0.7	98.7 [98.0, 99.3]	96.7 [95.3, 98.0]	95.6 [93.9, 97.3]
Reoperations	2	0.6	12	1.1	97.1 [96.2, 98.1]	95.1 [93.6, 96.6]	93.0 [90.9, 95.1]
Anticoagulant-related hemorrhage	2	0.6	9	0.8	97.1 [95.2, 99.0]	97.1 [95.2, 99.0]	94.1 [88.2, 100]
Endocarditis	1	0.3	3	0.3	99.0 [97.9, 100]	98.7 [97.4, 98.9]	98.7 [97.4, 98.9]
Hemolysis	0	0.0	1	0.1	99.7 [99.0, 100]	99.7 [99.0, 100]	99.7 [99.0, 100]
Nonstructural dysfunction	0	0.0	3	0.3	100 [100, 100]	99.3 [98.0, 100]	98.3 [95.9, 100]
Perivalvular leak (all)	1	0.3	5	0.5	98.4 [97.0, 99.8]	98.4 [97.0, 99.8]	97.3 [94.9, 99.8]
Structural valve deterioration	0	0.0	5	0.5	100.0 [100, 100]	97.6 [95.2, 100]	92.8 [85.3, 100]
Thromboembolism	5	1.4	8	0.7	97.5 [95.8, 99.2]	96.1 [93.8, 98.5]	96.1 [93.8, 98.5]
Thrombosis	0	0.0	0	0.0	100.0 [100, 100]	100.0 [100, 100]	100.0 [100, 100]

Notes:
1. Late event rates were calculated as linearized rates (%/pt-yr) based on 1072.5 late patient-years (> 30 days postoperatively).
2. Freedom from event rates were calculated using the Kaplan-Meier method. Greenwood's formula was used for calculation of the standard errors of these estimates.
3. n = numbers of patients.

9. SUMMARY OF NONCLINICAL STUDIES

9.1. Bench Testing

In vitro studies were performed for the Carpentier-Edwards PERIMOUNT Pericardial Bioprosthesis Model 6900 Mitral as recommended in the FDA's *Draft Replacement Heart Valve Guidance* (1994).

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9.1.1. Biocompatibility Studies

Biocompatibility tests were performed in accordance with the requirements of ISO 10993-1, with the exception of carcinogenicity and hemocompatibility testing. Carcinogenicity testing was determined to be unnecessary since the test articles demonstrated no mutagenic potential at levels at or above those intended for the clinical application. Device hemocompatibility was evaluated and found to be acceptable in animal implantation studies (refer to Section 9.2.1). All studies were performed by Edwards Lifesciences LLC, Irvine, CA in accordance with the FDA GLP Regulations (21 CFR 58). A matrix of the tests performed and the corresponding results are provided in Table 2.

Table 2: Biocompatibility Tests and Results

Test Performed	Test Objective	Samples: Control	Samples: CEP Mitral	Results
In vitro inhibition of cell growth	Assess the effect of the aqueous extract of a material on the normal growth of cells in culture. Sample is considered non-inhibitory to cell growth if percent of inhibition is ≤ 29%	Negative control only: Water	Silicone rubber	Non-inhibitory to cell growth.
			Elgiloy Alloy	Non-inhibitory to cell growth.
			Polyethylene terephthalate (PET) film, cloth, and thread	Non-inhibitory to cell growth.
			Polytetrafluoroethylene (PTFE) cloth and thread	Non-inhibitory to cell growth.
			PTFE impregnated PET thread	Non-inhibitory to cell growth.
			Black silk suture thread	Non-inhibitory to cell growth at a concentration representative of that used in the device. Inhibitory to cell growth at elevated sample concentrations.

Table 2: Biocompatibility Tests and Results (continued)

Test Performed	Test Objective	Samples: Control	Samples: CEP Mitral	Results
In vitro cytotoxicity (Medium eluate method)	Evaluate the cytotoxic effects of a material growth medium extract on a human fibroblast monolayer. The sample is judged non-cytotoxic if lysis is not greater than the negative control.	Negative Control: Cell growth medium Positive Control: Approximately 5% Ethanol in water	Silicone rubber	Non-cytotoxic to cells.
			Elgiloy Alloy	Non-cytotoxic to cells.
			PET film, cloth and thread	Non-cytotoxic to cells.
			PTFE cloth and thread	Non-cytotoxic to cells.
			PTFE impregnated PET thread	Non-cytotoxic to cells.
			Black silk suture thread	Non-cytotoxic at concentrations representative of that used in the device. Cytotoxic at concentrations above those used in the device.
In vitro cytotoxicity (Agar overlay assay)	Evaluate the cytotoxicity of diffusible components of a material through an agar overlay assay. The sample is judged non-cytotoxic if lysis is not greater than the negative control.	Negative control: Polypropylene solid sample Positive control: Polyvinyl chloride (PVC) with Organotin	Silicone rubber	Non-cytotoxic to cells.
			Elgiloy Alloy	Non-cytotoxic to cells.
			PET film, cloth and thread	Non-cytotoxic to cells.
			PTFE cloth and thread	Non-cytotoxic to cells.
			PTFE impregnated PET thread	Non-cytotoxic to cells.
			Black silk suture thread	Moderate to severe cytotoxicity (20 to 60% cell lysis) due to glutaraldehyde and formaldehyde residuals present in the samples and under static environments imposed in the test.

Table 2: Biocompatibility Tests and Results (continued)

Test Performed	Test Objective	Samples: Control	Samples: CEP Mitral	Results
In vitro mutagenicity (Sister chromatid exchange assay)	Detect the presence of mutagenic moieties in biomaterials using activated and non-activated systems.	Negative control: Distilled water or the corresponding medium used for the test article extraction Positive control (non-activated system): Distilled water with mitomycin C @ 0.005 µg/mL Positive control (activated system): Distilled water with cyclophosphamide @ 1.0 µg/mL	Silicone rubber	Non-mutagenic using activated and non-activated systems.
			Elgiloy Alloy	Non-mutagenic using activated and non-activated systems.
			PET film, cloth and thread	Non-mutagenic using activated and non-activated systems.
			PTFE cloth and thread	Non-mutagenic using activated and non-activated systems.
			PTFE impregnated PET thread	Non-mutagenic using activated and non-activated systems.
			Black silk suture thread	Non-mutagenic at all concentrations using the activated system and at concentrations representative of the final device using the non-activated system.
USP mouse systemic injection	Evaluate the systemic effect of a material extract in mice. The sample is considered systemically non-toxic if all the mice treated with the sample extract survive at the end of 72 hours and none . shows an outward symptom of greater reaction or weight change than mice treated with the negative control.	Negative control: Normal saline and vegetable oil or the corresponding medium used for the test article extraction	Silicone rubber	All mice normal. Non-toxic.
			Elgiloy Alloy	All mice normal. Non-toxic.
			PET film, cloth and thread	All mice normal. Non-toxic.
			PTFE cloth and thread	All mice normal. Non-toxic.
			PTFE impregnated PET thread	All mice normal. Non-toxic.
			Black silk suture thread	All mice normal. Non-toxic.

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Table 2: Biocompatibility Tests and Results (continued)

Test Performed	Test Objective	Samples: Control	Samples: CEP Mitral	Results
USP rabbit intracutaneous irritation	Evaluate the effects of a material extract in contact with the dermis of rabbits. The sample is considered non-irritating if the average erythema/edema rating for any given time is not remarkably greater than that for the negative control.	Negative control: Normal saline and vegetable oil or the corresponding medium used for the test article extraction	Silicone rubber	All rabbits normal. Non-irritating.
			Elgiloy Alloy	All rabbits normal. Non-irritating.
			PET film, cloth and thread	All rabbits normal. Non-irritating.
			PTFE cloth and thread	All rabbits normal. Non-irritating.
			PTFE impregnated PET thread	All rabbits normal. Non-irritating.
			Black silk suture thread	All rabbits normal. Non-irritating.
USP rabbit intramuscular implantation test (subchronic and chronic)	Evaluate the effect of direct exposure of the test material when implanted into the paravertebral muscle of rabbits for 7, 30, 60, or 90 days. A material is biocompatible if there is no gross visible evidence of tissue damage and if histopathological examination shows no signs of chemical-induced cytotoxicity.	Negative control: Polyethylene 306	Silicone rubber	Material is biocompatible (sub-chronic and chronic evaluations) with no signs of chemical-induced cytotoxicity.
			Elgiloy Alloy	Material is biocompatible (sub-chronic and chronic evaluations) with no signs of chemical-induced cytotoxicity.
			PET film, cloth and thread	Material is biocompatible (sub-chronic and chronic evaluations) with no signs of chemical-induced cytotoxicity.
			PTFE cloth and thread	Material is biocompatible (sub-chronic and chronic evaluations) with no signs of chemical-induced cytotoxicity.
			PTFE impregnated PET thread	Material is biocompatible (sub-chronic and chronic evaluations) with no signs of chemical-induced cytotoxicity.
			Black silk suture thread	Material is biocompatible (sub-chronic and chronic evaluations) with no signs of chemical-induced cytotoxicity.
Guinea pig maximization test	Evaluate the potential of a material to produce sensitization when the material saline extract is repeatedly exposed to guinea pigs. Material is considered to possess no apparent sensitizing properties if the erythema and edema score are not remarkably greater than the negative control.	Negative control: Normal saline and vegetable oil or the corresponding medium used for the test article extraction	Silicone rubber	All guinea pigs normal. Non-sensitizing.
			Elgiloy Alloy	All guinea pigs normal. Non-sensitizing.
			PET film, cloth and thread	All guinea pigs normal. Non-sensitizing.
			PTFE cloth and thread	All guinea pigs normal. Non-sensitizing.
			PTFE impregnated PET thread	All guinea pigs normal. Non-sensitizing.
			Black silk suture thread	All guinea pigs normal. Non-sensitizing.

9.1.2. Hydrodynamic Performance

In vitro hydrodynamic performance studies of the Carpentier-Edwards PERIMOUNT Pericardial Bioprosthesis Model 6900 Mitral were performed in accordance with testing recommendations outlined in the FDA's *Draft Replacement Heart Valve Guidance* (1994), ISO 5840:1996 *Cardiovascular Implants-Cardiac Valve Prostheses*, and CEN/TC 285 *Non-Active Surgical Implants-Part 1. Heart Valve Substitutes*. A 29 mm Carpentier-Edwards® Bioprosthesis (CEBP) Mitral Model 6625 porcine valve was used as a reference in studies requiring concurrent testing of a tissue valve marketed in the U.S. All test and reference valves were final production samples. A matrix of the hydrodynamic tests performed and the results are provided in Table 3.

Table 3: Hydrodynamic Testing and Results

Test	Sample Size: PERIMOUNT Pericardial	Sample Size: Reference Valve (CEBP)	Results
Steady Forward Flow Pressure Drop	3 of each size	1 - 29 mm	The size 29 mm CEP mitral valves showed a lower pressure drop and a greater effective orifice area compared to the size 29 mm reference valve.
Steady Backflow Leakage Testing	3 of each size	1 - 29 mm	The size 29 mm CEP mitral valves exhibited higher leakage under steady back flow pressure when compared to the size 29 mm reference valves.
Pulsatile Flow Pressure Drop	3 of each size	1 - 29 mm	The size 29mm CEP mitral valves exhibited lower pressure drops and larger effective orifice areas than the size 29 mm reference valve.
Pulsatile Flow Regurgitation	3 of each size	1 - 29 mm	Because the leakage rates for the size 29mm CEP mitral and reference valves were generally low, the total regurgitant volumes for each valve remained relatively constant at the tested cardiac outputs regardless of beat rate.
Flow Visualization	1 - 25 mm	N/A	Results showed a broad central jet-like flow during valve opening, with no evidence of flow stasis during valve opening or closure.
Verification of the Bernoulli Relationship	3 of each size	N/A	Transvalvular pressure drops obtained by Doppler ultrasonography and transducer showed good correlation. Use of the coefficient 4 in conjunction with Doppler-derived velocities in the modified Bernoulli equation provides an accurate and consistent estimation of transvalvular pressure gradients.

N/A = not applicable

9.1.3. Structural Performance

In vitro structural performance (accelerated wear and fatigue) studies of the Carpentier-Edwards PERIMOUNT Pericardial Bioprosthesis Model 6900 Mitral were performed in accordance with testing recommendations outlined in the FDA's *Draft Replacement Heart Valve Guidance* (1994), ISO 5840:1996 *Cardiovascular Implants - Cardiac Valve Prostheses*, and CEN/TC 285 *Non-Active Surgical Implants - Part 1. Heart Valve Substitutes*. Size 25 and 29 mm Carpentier-Edwards® Bioprostheses (CEBP) Model 6625 Mitral (porcine) were used as references in studies requiring concurrent testing of a tissue valve marketed in the U.S. All test and reference

valves were final production samples. A matrix of the structural performance tests performed on the device is provided in Table 4.

Table 4: Structural Performance Testing and Results

Test	Sample Size: PERIMOUNT Pericardial	Reference Valve Sample Size	Results
Accelerated Wear Testing	4 of each - 25 and 29 mm 3 of each - 31 and 33 mm	2 each – 25 and 29 mm	Two of the test valves (sizes 29 and 33 mm) and one reference valve (size 29 mm) exhibited significant regurgitation at the conclusion of the test; none were the result of wireform fracture. All other valves functioned normally throughout the duration of the test.
Dynamic Failure Mode Testing	1 of each - 25, 29, 31, and 33 mm	1 each – 25 and 29 mm	All valves failed due to incompetence at pressures of 200 to 400 mmHg. Reference valves sustained cycles to failure similar to the test valves.
Stress Analysis	Sizes 31 and 33 mm wireforms	N/A	The stent sizes demonstrating the highest stresses were tested. The results demonstrate that the peak stresses are 56.80 ksi (tensile) and 56.97 ksi (compressive) for size 31 mm and 62.64 ksi (tensile) and 62.64 ksi (compressive) for size 33 mm.
Fatigue Lifetime Determination	Sizes 31 and 33 mm wireforms	N/A	The results of the fatigue lifetime determination demonstrate that the worst-case valve sizes (31 and 33 mm) have a predicted lifetime ≥ 15 years.
Sewing Ring Integrity	3 of each - 25, 27, 29, 31, and 33 mm sewing rings	N/A	Sewing ring integrity results demonstrated that the sewing ring remains structurally intact under simulated implant conditions.

N/A = not applicable

9.2. Animal Studies

9.2.1. Valve Implantation Studies

Two (2) chronic *in vivo* animal implantation studies were conducted using Carpentier-Edwards PERIMOUNT Pericardial Model 6900 Mitral valves implanted in a healthy juvenile sheep model. A total of 10 valves (sizes 25 mm [n = 6] and 27 mm [n = 4]) were implanted in the mitral position for a total of 5 months. All 10 animals remained healthy throughout the 5-month in-life period. The animals demonstrated no clinical signs indicative of valve-related abnormalities over the 20-week evaluation period.

Parameters evaluated during the study included physical observations, surgical implant observations, hematology and blood chemistry measurements (prior to implant and at explant), cardiac output and peak transvalvular gradients (at explant only), explant valve analysis for calcium and phosphate content, necropsy observations, and histopathological evaluation of selected organs and of the explanted valve and host tissue.

Clinical Chemistry and Hematology

Hematology and blood chemistry measurements were within normal limits for the age and size of the sheep evaluated.

Hemodynamic Performance

Cardiac outputs and peak transvalvular gradient measurements conducted at explant were within normal limits for the age and size of the sheep evaluated (cardiac output: 4.5 ± 0.9 L/min; peak gradient: 13 ± 8 mmHg [mean ± std. dev.]). Left ventricular catheterization and angiography performed at explant on 5 sheep showed no detectable regurgitation in 3 of the 5 sheep; narrow regurgitant jets of slight density (1+ regurgitation) were observed in 2 of the 5 sheep.

Histopathology

All surviving animals were sacrificed at approximately 20 weeks post-implant. Selected systemic organs were grossly examined and microscopically evaluated; no untoward effects were noted. The bioprosthetic valve and sheep host tissue were explanted and x-rayed for appearance prior to being microscopically examined. Histopathologically, there was evidence of calcification in 4 of the 10 sheep.

Anticalcification Treatment Effectiveness

Samples of the explanted bioprosthetic valve leaflets and the sheep native tissue were evaluated for calcification by measuring calcium (Ca) and phosphate (PO_4) content. The measured values were not considered significant unless they were 1% or greater over the background measurement. All results were under this threshold except for leaflet samples from 2 sheep. Of the 10 valves, 2 valves (20%) had elevated quantitative calcium content versus the remaining 8 valves after 20 weeks of implantation. The measured levels (mean ± std. dev.) of calcium and phosphate in the explanted leaflet tissue were 23.6 ± 43.1 mg calcium/g dry tissue weight and 21.2 ± 23.5 mg PO_4/g dry tissue weight.

Handling Characteristics

All valves were sewn in with relative ease and observed to have good coaptation and fit within each annulus.

9.2.2. Subcutaneous Implantation Studies

Two (2) *in vivo* subcutaneous implantation studies in rats and rabbits were performed. Bovine pericardial tissue exposed to the Edwards Lifesciences XenoLogiX process (fixation in glutaraldehyde, processing in a solution containing ethanol and polysorbate 80 [a surfactant], and packaging in glutaraldehyde) was tested against tissue exposed to glutaraldehyde only. Samples were implanted into subcutaneous pockets created in weanling rats approximately 24 to 28 days of age and into juvenile rabbits approximately 8 weeks of age. Implant duration ranged from approximately 30 days to 90 days from the date of implantation. After explant, samples were evaluated for x-ray evaluation, histological evaluation, and quantitative elemental results. The results indicate that bovine pericardial tissues exposed to the Edwards Lifesciences XenoLogiX process show a statistically significant reduction in calcification potential when compared to samples that were exposed to the glutaraldehyde fixation process alone ($p < 0.05$). The clinical significance of these study results is unknown. A matrix of the subcutaneous implant studies performed is provided in Table 5.

Table 5: Subcutaneous Implant Study Results

Study and Test Parameter	Results: PERIMOUNT Pericardial Tissue (n = 3)	Results: Glutaraldehyde Pericardial Tissue (n = 3)	Statistical Analysis Results
90-Day Rat Subcutaneous Implant Study			
X-ray evaluation[1]	0.0 ± 0.0	3.0 ± 0.0	$p < 0.05$
Histological evaluation[2]	0.3 ± 0.9	4.9 ± 0.3	$p < 0.05$
Elemental analyses[3]	Calcium: 4.4 ± 14 Phosphate: 9.8 ± 23	Calcium: 255 ± 16 Phosphate: 350 ± 22	$p < 0.05$ $p < 0.05$
90-Day Rabbit Subcutaneous Implant Study			
X-ray evaluation[1]	1.7 ± 1.1	3.0 ± 0.0	$p < 0.05$
Histological evaluation[2]	1.3 ± 1.0	3.6 ± 0.5	$p < 0.05$
Elemental analyses[3]	Calcium: 69 ± 56 Phosphate: 94 ± 76	Calcium: 234 ± 21 Phosphate: 320 ± 20	$p < 0.05$ $p < 0.05$

Notes:

1. Explanted tissue is examined by x-ray and graded for degree of calcification: 0 = none; 1 = mild; 2 = moderate; 3 = severe. Statistical analyses between groups performed using the Wilcoxon rank sum test.
2. Explanted tissue is Von Kassa stained and examined histologically for the presence of calcium phosphate: 0=negative; 1 = minimal; 2 = mild; 3 = moderate; 4 = marked; 5 = severe. Statistical analyses between groups performed using the Wilcoxon rank sum test.
3. Explanted tissue is analyzed for calcium and phosphate content. Results are reported as mg calcium (or phosphate) per g dry tissue weight. Statistical analyses between groups performed using a two-sided t-test.

9.3. Sterilization

The Carpentier-Edwards PERIMOUNT Pericardial Bioprosthesis Model 6900 Mitral is terminally sterilized in buffered glutaraldehyde solution. After terminal sterilization, the product is held in quarantine until sterility is verified per process specifications. Requalification of the process is performed quarterly.

Resterilization and cleaning of the accessory components (stainless steel sizer/handles and polysulfone sizers) was validated using artificial blood soil inoculated with *B. stearothermophilus*. A 2-3 log reduction was achieved by the cleaning method, and sub-lethal flash, pre-vacuum, and gravity displacement cycles using different temperatures. Spore log reductions ranged from 13.6 to 30.0, depending on method used.

9.4. Shelf Life

Both packaging and product integrity studies were conducted to ensure that the shelf life for the package and product is maintained for a minimum of 4 years. Packaging integrity studies (microbial challenge) consisted of real-time and accelerated aging, whereas product integrity samples underwent real-time aging.

9.4.1. Package Integrity

The integrity of the valve packaging components was evaluated after exposure to the maximum steam sterilization cycles and terminal liquid sterilization process. Package integrity testing consisted of physical (leak and glutaraldehyde packaging solution concentration) and sterility testing before and after exposure to glutaraldehyde in an elevated temperature condition, and after a simulated shipping process. Accelerated aging results simulating 0, 1, and 4 years real-time demonstrated package integrity throughout the 4-year shelf life period. Packaging validation studies conducted after maximum exposure to the terminal liquid sterilization process demonstrated that this sterilization method does not adversely affect package integrity.

9.4.2. Product Integrity

Non-biological Component Shelf Life

Stent components were evaluated by functional testing of the individual non-biological materials after 4 years of real-time storage in glutaraldehyde. The results demonstrated that storage in glutaraldehyde up to 4 years has minimal effect on the properties and functions of the individual non-biological materials used in the bioprosthesis.

Tissue Shelf Life

Bovine pericardial tissue stability and storage solution adequacy were evaluated using 3 parameters: shrinkage temperature, moisture content, and glutaraldehyde concentration. Tissue samples subjected to real-time aging were evaluated at designated intervals for shrinkage temperature and moisture content. Glutaraldehyde content of the storage solution was determined by glutaraldehyde assay.

The results demonstrated that the tissue shrinkage temperature is stable over time at the recommended storage temperature of 4° to 25°C for a duration exceeding the 4-year shelf life. The effects of storage time on the moisture content were monitored because chemical changes in the tissue could affect the hydration level of the tissue. A gradual decrease in moisture content with time was seen, with a more rapid decline at higher temperatures. Glutaraldehyde assays showed the expected trend of a gradual increase in concentration over time, with a more rapid increase at higher storage temperatures. Acceptable levels of glutaraldehyde concentration were maintained for the 4-year shelf life period in the recommended storage temperature range of 4° to 25°C. These results demonstrate product integrity to 4 years.

10. SUMMARY OF CLINICAL STUDIES

The safety endpoints captured in the prospective studies were complications; blood analyses were used to confirm the absence or presence of certain complications. The safety results are provided above in Table 1. Effectiveness endpoints were New York Heart Association (NYHA) functional classification and echocardiographic assessments. Preoperative and operative patient demographics are presented below, followed by the effectiveness results.

Table 6: Preoperative Patient Demographics

Variable	Category	Study Characteristics (N = 363; 1100 total pt-yrs.)	
		n	% (n/N)[1]
Age at implant	Mean ± SD	363	66.1 ± 10.7
Gender	Female	212	58.4%
	Male	151	41.6%
NYHA Classification	I	11	3.0%
	II	73	20.1%
	III	192	52.9%
	IV	84	23.1%
	Not Reported	3	0.8%
Diagnosis	None	30	8.3%
	Stenosis	91	25.1%
	Regurgitation	184	50.7%
	Mixed Disease	58	16.0%

Note:
1. n = number of patients in each category; N = total number of study patients

Table 7: Operative Patient Demographics

Variable	Category	Study Characteristics (N = 363; 1100 total pt-yrs.)	
		n	% (n/N)[1]
Etiology[2]	Rheumatic Heart Disease	135	37.2%
	Calcification	82	22.6%
	Degeneration	50	13.8%
	Endocarditis	39	10.7%
	Failed Bioprosthesis	15	4.1%
	Ischemic Heart Disease	14	3.9%
	Congenital Abnormalities	8	2.2%
	Other	44	12.1%
Concomitant Procedures[2]	None	200	55.1%
	CABG[3]	78	21.5%
	Tricuspid Repair	61	16.8%
	Intra-Aortic Balloon Pump	17	4.7%
	Pacemaker[4]	6	1.7%
	Aortic Repair/Replacement	5	1.4%
	Aneurysm Repair	4	1.1%
	Other	31	8.5%
Pre-existing Conditions[2]	None	122	33.6%
	CAD[5]/CABG	72	19.8%
	Hypertension	61	16.8%
	Atrial Fibrillation	53	14.6%
	Previous MI[6]	45	12.4%
	Cerebrovascular Disease	36	9.9%
	Other	234	64.5%
Valve Size (mm)	25	22	6.1%
	27	110	30.3%
	29	137	37.7%
	31	81	22.3%
	33	13	3.6%

Notes:
1. n = number of patients in each category; N = total number of study patients
2. May be more than one per patient
3. CABG = Coronary Artery Bypass Graft Surgery
4. Permanent or temporary
5. CAD = Coronary Artery Disease
6. MI = Myocardial Infarction

Table 8: Effectiveness Outcomes, Functional NYHA

NYHA Functional Class	Preoperative Assessment		Postoperative Assessments			
			1 to 2 Year		5 Year	
	n/N[1]	%	n/N	%	n/N	%
I	11/363	3.0	120/268	44.8	40/129	31.0
II	73/363	20.1	90/268	33.6	25/129	19.4
III	192/363	52.9	15/268	5.6	1/129	0.8
IV	84/363	23.1	0/268	0.0	0/129	0.0
Not Available	3/363	0.8	43/268	16.0	63/129	48.8

Note:
1. n = number of patients in each category; N = total number of study patients

Table 9: Effectiveness Outcomes, Hemodynamic Results[1]

Hemodynamic Parameter	Results By Valve Size				
	25 mm	27 mm	29 mm	31 mm	33 mm
[redacted]					
Mean Gradient[4]	n = 3	n = 23	n = 36	n = 23	n = 3
• mean ± sd	5.7 ± 1.2	4.2 ± 1.7	4.2 ± 1.7	3.6 ± 1.0	7.5 ± 5.8
• min, max	5, 7	2, 9	1, 8	2, 5	3, 14
EOA[5]	n = 1	n = 17	n = 22	n = 25	n = 5
• mean ± sd	1.5	2.9 ± 0.9	3.1 ± 0.9	2.5 ± 0.7	3.0 ± 1.2
• min, max	1.5, 1.5	1.3, 4.1	1.4, 4.2	1.5, 3.8	1.6, 4.9
Regurgitation[6]	n = 3	n = 28	n = 51	n = 40	n = 8
0	3/3 (100%)	22/28 (79%)	36/51 (71%)	30/40 (75%)	4/8 (50%)
1+	0/3 (0%)	5/28 (18%)	13/51 (25%)	7/40 (18%)	4/8 (50%)
2+	0/3 (0%)	0/28 (0%)	1/51 (2%)	3/40 (7%)	0/8 (0%)
3+	0/3 (0%)	0/28 (0%)	1/51 (2%)	0/40 (0%)	0/8 (0%)
4+	0/3 (0%)	0/28 (0%)	0/51 (0%)	0/40 (0%)	0/8 (0%)
Not Available	0/3 (0%)	1/28 (3%)	0/51 (0%)	0/40 (0%)	0/8 (0%)
[redacted]					
Mean Gradient[4]	n = 5	n = 19	n = 15	n = 5	n = 2
• mean ± sd	6.4 ± 1.7	5.3 ± 5	3.4 ± 1.2	4 ± 1.9	4 ± 0
• min, max	5, 9	2, 25	2, 6	2, 7	4, 4
EOA[5]	n = 5	n = 18	n = 13	n = 5	n = 2
• mean ± sd	2.9 ± 0.8	2.6 ± 0.7	2.8 ± 0.6	2.9 ± 0.3	2.6 ± 1
• min, max	1.8, 3.6	1.5, 5	2, 3.8	2.4, 3.3	2, 3.3
Regurgitation[6]	n = 5	n = 21	n = 15	n = 6	n = 2
0	3/5 (60%)	17/21 (81%)	6/15 (40%)	4/6 (67%)	1/2 (50%)
1+	0/5 (0%)	4/21 (19%)	8/15 (53%)	2/6 (33%)	0/2 (0%)
2+	1/5 (20%)	0/21 (0%)	1/15 (7%)	0/6 (0%)	1/2 (50%)
3+	0/5 (0%)	0/21 (0%)	0/15 (0%)	0/6 (0%)	0/2 (0%)
4+	1/5 (20%)	0/21 (0%)	0/15 (0%)	0/6 (0%)	0/2 (0%)
Not Available	0/5 (0%)	0/21 (0%)	0/15 (0%)	0/6 (0%)	0/2 (0%)

Notes:
1. Hemodynamic evaluations were performed using transthoracic echocardiography (TTE) and in some cases, transesophageal echocardiography (TEE).
2. MVR = Mitral valve replacement
3. DVR = Double valve replacement
4. Mean Gradient in mm Hg.
5. EOA= Effective Orifice Area, cm^2
6. Regurgitation = none, 0; mild, 1+; moderate, 2+; moderate/severe, 3+; severe, 4+

Table 9: Effectiveness Outcomes, Hemodynamic Results (continued)[1]

Hemodynamic Parameter	Results By Valve Size				
	25 mm	27 mm	29 mm	31 mm	33 mm
[illegible]					
Mean gradient[4]	n = 3	n = 40	n = 47	n = 27	n = 4
• mean ± sd	5.2 ± 0.7	4.1 ± 1.6	3.5 ± 1.8	3.1 ± 1.4	2.1 ± 0.5
• min, max	4.7, 6	1, 7	1, 10	1,7	1.5, 2.7
EOA[5]	n = 2	n = 35	n = 46	n = 29	n = 5
• mean ± sd	1.8 ± 0.4	2.3 ± 0.6	2.6 ± 0.5	2.6 ± 0.7	2.5 ± 0.5
• min, max	1.5, 2.0	1.2, 3.5	1.1, 3.7	1.1, 3.7	2.1, 3.2
Regurgitation[6]	n = 4	n = 42	n = 51	n = 29	n = 5
0	2/4 (50%)	31/42 (74%)	36/51 (71%)	17/29 (59%)	3/5 (60%)
1+	1/4 (25%)	9/42 (21%)	11/51 (21%)	8/29 (27%)	1/5 (20%)
2+	1/4 (25%)	2/42 (5%)	4/51 (8%)	2/29 (7%)	1/5 (20%)
3+	0/4 (0%)	0/42 (0%)	0/51 (0%)	2/29 (7%)	0/5 (0%)
4+	0/4 (0%)	0/42 (0%)	0/51 (0%)	0/29 (0%)	0/5 (0%)
Not Available	0/4 (0%)	0/42 (0%)	0/51 (0%)	0/29 (0%)	0/5 (0%)
[illegible]					
Mean gradient[4]	n = 0	n = 6	n = 5	n = 0	n = 0
• mean ± sd	N/A[7]	8.8 ± 8.1	5.0 ± 2.3	N/A	N/A
• min, max	N/A	4, 25	3, 8	N/A	N/A
EOA[5]	n = 0	n = 2	n = 4	n = 0	n = 0
• mean ± sd	N/A	2.0 ± 1.5	2.9 ± 0.6	N/A	N/A
• min, max	N/A	1.0, 3.1	2.1, 3.5	N/A	N/A
Regurgitation[6]	n = 0	n = 6	n = 5	n = 0	n = 0
0	0/0 (0%)	4/6 (66%)	2/5 (40%)	0/0 (0%)	0/0 (0%)
1+	0/0 (0%)	1/6 (17%)	3/5 (60%)	0/0 (0%)	0/0 (0%)
2+	0/0 (0%)	1/6 (17%)	0/5 (0%)	0/0 (0%)	0/0 (0%)
3+	0/0 (0%)	0/6 (0%)	0/5 (0%)	0/0 (0%)	0/0 (0%)
4+	0/0 (0%)	0/21 (0%)	0/5 (0%)	0/0 (0%)	0/0 (0%)
Not Available	0/0 (0%)	0/21 (0%)	0/5 (0%)	0/0 (0%)	0/0 (0%)

Notes:
1. Hemodynamic evaluations were performed using transthoracic echocardiography (TTE) and in some cases, transesophageal echocardiography (TEE).
2. MVR = Mitral valve replacement
3. DVR = Double valve replacement
4. Mean gradient in mm Hg.
5. EOA = Effective Orifice Area, cm^2
6. Regurgitation = none, 0; mild, 1+; moderate, 2+; moderate/severe, 3+; severe, 4
7. N/A = Not available

10.1. Description of Patients and Analysis for Gender Bias

A gender bias was not found in the Edwards Lifesciences clinical studies.

Of the 363 patients followed in the clinical studies, 58% were female and 42% were male. This gender distribution is consistent with the incidence of patients presenting for mitral valve replacement in the U.S. The log-rank test was used to compare all adverse event outcomes by gender. No significant difference in outcomes between males and females were noted for any adverse event. Therefore, the results for valve-related adverse events following mitral valve replacement are representative of both men and women.

11. RISK-BENEFIT ANALYSIS

Laboratory and clinical data provide reasonable assurance that the Carpentier-Edwards PERIMOUNT Pericardial Bioprosthesis Model 6900 Mitral is safe and effective when used according to the approved labeling.

12. CONCLUSIONS DRAWN FROM THE STUDIES

The results from pre-clinical laboratory studies performed on the Carpentier-Edwards PERIMOUNT Pericardial Bioprosthesis Model 6900 Mitral for biocompatibility testing, hydrodynamic performance testing (steady forward flow pressure drop, steady backflow leakage testing, pulsatile flow pressure drop, pulsatile flow regurgitation, flow visualization, and verification of the Bernoulli Relationship), and structural performance testing (accelerated wear testing, dynamic failure mode testing, stress analysis, fatigue lifetime determination, and sewing ring integrity testing) demonstrate that this device is suitable for long-term implant.

The animal studies show that the Carpentier-Edwards PERIMOUNT Pericardial Bioprosthesis Model 6900 Mitral is safe for valve replacement.

The clinical studies submitted in the PMA provide sound scientific evidence that the Carpentier-Edwards PERIMOUNT Pericardial Bioprosthesis Model 6900 Mitral is safe and effective for the replacement of native or prosthetic mitral valves.

13. PANEL RECOMMENDATIONS

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory Systems Device Panel, a FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

14. FDA DECISION

FDA issued an approval order on _____.

The applicant's manufacturing and control facilities were inspected July 28, 2000, and the facilities were found to be in compliance with the Good Manufacturing Practices (GMP) regulation.

15. APPROVAL SPECIFICATIONS

Directions for use: See Final Draft Labeling (Instructions for Use).

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the Final Draft Labeling (Instructions for Use).

Post-approval Requirements and Restrictions: See Approval Order.